release from the fibers electrospun from a solution containing PGA:PLA copolymer and collagen to which 100 ng of VEGF were added. Results demonstrate not only that the matrix releases VEGF in PBS but also that cross-linking with glutaraldehyde slows release from the matrix.

EXAMPLE 4

Polyethylene-co-vinyl acetate) (PEVA) was a gift from DuPont (Elvax 40, 40 vinyl acetate). PEVA pellets were soaked in ethanol for several days to remove antioxidants. Poly(lactic acid) (100 L PLA) was a gift from by Alkermes, Inc. (Medisorb®) with a number-average molecular weight, M_n, of 205 KD and polydispersity of 1.7. All solvents were analytical grade and were used as received. Tris(hydroxymethyl)aminomethane hydrochloride (Trizma® HCl) and trishydroxymethylaminomethane (Trizma®-base) were supplied by Sigma and were used without further purification to prepare buffer solutions of pH 7.35. Tetracycline hydrochloride was also obtained from Sigma. Actisite® periodontal fiber (0.5rrim PEVA) containing 25wt% tetracycline hydrochloride was a gift from Alza Corporation (Palo Alto, CA).

Electrospinning was carried out using 14 % wt/v solutions of 100% PEVA, 100% PLA, or mixtures of the two in chloroform. The mixtures used were 25% PEVA/75% PLA, 50%/50% of each, and 75% PEVA/25% PLA, with percentages by weight. Tetracycline hydrochloride, which is insoluble in chloroform, was solubilized in a small amount of methanol and added to the polymer solutions prior to electrospinning. The resulting solutions were yellow but clear, indicating homogeneous solubilization of both the polymers and drug.

The electrospinning set-up consisted of a glass pipette (held parallel to ground or angled at 45° downward), 0.32 mm diameter silver-coated copper wire (positive lead), a copper sheet (ground electrode) ca. 30 cm from the pipette, and a Spellman CZE100OR high voltage supply. A positive voltage (15 kV) was applied through the copper wire to the polymer solution inside the glass pipette. The solutions were delivered via syringe pumps to control the mass flow rate, which ranged from 10-18 ml/h. More conveniently, the solution can be held in a plastic syringe with the high voltage supply connected to the metal syringe needle. The solutions were delivered via syringe pumps to control the mass flow

rate, which ranged from 10-18 ml/h. The resulting electrically charged fibers were collected on a rotating metal plate to produce a sheet of non-woven fabric.

A 100L PLA containing 5% tetracycline hydrochloride (by weight) was electrospun from 14% W/V solution in chloroform, with a mass flow rate of the polymer solution between 18-21 ml/h. PEVA containing 5% tetracycline hydrochloride (expressed herein as by weight of total polymer) was electrospun from 14 % W/V solution with a mass flow rate of 3 ml/h. Blends containing 5% tetracycline hydrochloride and consisting of 25% PLA and 75% PEVA were electrospun at mass flow rates of 13-18 ml/h. A 50/50 PLA/PEVA blend with 5% tetracycline hydroxide was spun at a mass flow rate of 10-13 ml/h. A 50/50 PLA/PEVA blend with 25% tetracycline hydroxide (by weight of total polymer weight) was spun at a mass flow rate of 15ml/hr. A blend containing 75/25 PLA/PEVA with 5% tetracycline hydroxide was spun with a mass flow rate of 17 ml/h. The collected 'fabric' was used for studying the release of tetracycline hydrochloride.

For comparative purposes, cast films were made from different compositions of PLA and PEVA. As with the fibers, films were made of 25% PEVA/75% PLA, 50%/50% of each, and 75% PEVA/25% PLA and 5% tetracycline hydrochloride was added to each. The solutions in chloroform were cast onto glass petri dishes, left at room temperature until the chloroform was evaporated, then dried at 25 °C under vacuum for 3 hours. The release of tetracycline hydrochloride from ACTISITE® (PEVA) periodontal fiber was also compared.

Release of tetracycline hydrochloride was determined using UV-VIS measurements carried out at Perkin-Elmer UV/VIS Lambda 40 Spectrophotometer. The molar extinction coefficient for tetracycline hydrochloride in Tris buffer was found to be 15,800 from a linear Beer-Lambert plot of absorbance at 360 nm vs. concentration. Release of tetracycline hydrochloride was determined by placing a known mass of polymer and drug in tris buffer and monitoring the absorbance at 360 nm as a function of time. The buffer solution was changed if the released drug gave absorbance higher than 2.0. Data are reported as the % tetracycline hydrochloride released based upon the expected amount in the samples from the feed composition. The morphology of the electrospun samples were studied with JSM-820 Scanning electron microscope (JEOL Ltd.).

The release profiles of tetracycline hydrochloride from electrospun fibers and the cast films are shown in Figures 5 and 6. In Figure 5, the solid diamonds denote release from the fibers electrospun from the solution in which the polymer was 50% EVA and 50% PLA and 5% tetracycline was added. The open circles denote release from the fibers electrospun from the solution in which the polymer was 50% EVA and 50% PLA and 25% tetracycline was added. The open triangles denote release from the fibers electrospun from the solution in which the polymer was 100% PLA and 5% tetracycline was added. The solid squares denote release from the fibers electrospun from the solution in which the polymer was 100% EVA and 5% tetracycline was added.

In Figure 6, the open diamonds denote release from the fibers electrospun from the solution containing 100% EVA. The open squares denote release from the ACTISITE® (PEVA) periodontal fiber. The open triangles denote release from the film in which the polymer was 50% PLA and 50% PEVA. The open circles denote release from the film in which the polymer was 25% PLA and 75% PEVA. The solid diamonds connected by a thick line denote release from the film containing 100% PLA. The solid triangles denote release from the film in which the polymer was 75% PLA and 25% PEVA. The solid squares denote release from the fibers electrospun from the solution containing 25% PLA and 75% PEVA. The solid diamonds connected by a thin line denote release from film containing 100% EVA.

Electrospun EVA showed a higher release rate than the mats derived from PLA/EVA (50/50) or pure PLA. Electrospun PEVA released 65% of its drug content within 100 hours, whereas the electrospun 50/50 mixture of PEVA and PLA released about 40% over the same time period. Mats of PLA fibers with no PEVA exhibit some instantaneous release, with negligible release over 50 hours. The 50:50 sample with 25wt% tetracycline hydrochloride releases the drug more rapidly than the 5% sample, although the % released of the former approaches that of the latter after 150 hrs.

Figure 7 shows release profiles of three electrospun PEVA samples, two from the same batch of mat and another from a different preparation under identical conditions. The release amounts of each sample are denoted by solid diamonds, solid squares, and open triangles, respectively. The profiles are quite similar indicating very good reproducibility. In general, the initial rate of release of all formulations including ACTISITE® (denoted as Alza) is high during the